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## Orosomucoid-like protein 3, rhinovirus and asthma

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### Abstract

The genetic variants of orosomucoid-like protein 3 (*ORMDL3*) gene are associated with highly significant increases in the number of human rhinovirus (HRV)-induced wheezing episodes in children. Recent investigations have been focused on the mechanisms of *ORMDL3* in rhinovirus infection for asthma and asthma exacerbations. *ORMDL3* not only regulates major human rhinovirus receptor intercellular adhesion molecule 1 expression, but also plays pivotal roles in viral infection through metabolisms of ceramide and sphingosine-1-phosphate, endoplasmic reticulum (ER) stress, ER-Golgi interface and glycolysis. Research on the roles of *ORMDL3* in HRV infection will lead us to identify new biomarkers and novel therapeutic targets in childhood asthma and viral induced asthma exacerbations.

**Key Words:** Asthma; Intercellular adhesion molecule 1; Orosomucoid-like protein 3; Rhinovirus infection; Sphingolipids

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**Core tip:** Orosomucoid-like protein 3 (*ORMDL3*) gene has been identified to have a strong association with childhood asthma. The gene has also been found to link with human rhinovirus (HRV) infection in children. *ORMDL3* mediates HRV infection through regulating expression of HRV receptor intercellular adhesion molecule 1, metabolisms of ceramide and sphingosine-1-phosphate, endoplasmic reticulum (ER) stress, ER-Golgi interface and glycolysis.

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## INTRODUCTION

Asthma is one of the major health and economic burdens in the world. It is a syndrome characterised by airway inflammation and intermittent symptoms of wheeze and shortness of breath. The combinations of genetic and environment factors cause the disease[1]. The disease has a high prevalence as well as a chronic relapsing course. Acute asthma exacerbations are the major cause of high morbidity and mortality whilst severe asthma remains difficult to treat.

In 2007, single nucleotide polymorphisms (SNPs) flanking *ORMDL3* gene on chromosome 17 were found to be highly associated with asthma in a genome-wide association study[2]. This association has subsequently been replicated in many studies, including a multi-ancestry global meta-analysis[3]. The locus has also been found to be associated with many asthma related traits. Expression quantitative trait loci analysis revealed that SNPs in the locus regulate transcript levels of potential asthma genes[4]. The locus is associated with eosinophil account in blood and fractional exhaled nitric oxide levels[5]. *ORMDL3* locus is now considered as the major predisposing factor for childhood-onset asthma. Children with enhanced transcription genotypes at *ORMDL3* locus have been found to have significant increases in the number of wheezing illnesses. Early symptomatic human rhinovirus (HRV) infection is a risk factor for subsequent asthma, and the infection causes nearly two thirds of childhood asthma exacerbations[6]. The genetic variants on chromosome 17q21 and early environmental tobacco smoke exposure enhance the association between early respiratory infection and early-onset asthma. Individuals who were homozygous for the risk alleles at the *ORMDL3*-associated SNPs had a greater than twofold difference in the association between early viral infection and asthma[7].

The symptoms of viral respiratory infection are most caused by rhinoviruses[8]. More than twenty years ago, as the development of molecule techniques of identifying pathogens, rhinoviruses were found to be the major virus types in mild and severe wheezing illness in all age groups of children, but particularly over one year of age[9]. The most common symptoms for HRV infection include rhinorrhea, sore throat, nasal congestion, sneezing, cough, and headache[10]. HRV infection is also the major cause for exacerbations of chronic obstructive pulmonary disease (COPD) and cystic fibrosis [11,12]. In this review, I will update the recent developments for research on potential mechanisms that *ORMDL3* regulates HRV infection in asthma. I will also discuss the research strategies to identify novel therapeutic targets for HRV infection in human airway diseases.

## HRVS

HRVs were identified in the 1950s for exploring the causes of the common cold[13,14] and are positive-sense, single-stranded-RNA (ssRNA) viruses with approximate 7200 base pairs. The viruses belong to the family *Picornaviridae* and the genus enterovirus. The genome consists of a single gene whose translated a protein peptide. The protein peptide then is cleaved by protease to 11 proteins[15]. Among them, four proteins including VP1, VP2, VP3, and VP4 consist the viral capsid encasing the RNA genome, while the rest are non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, 3D) for functioning in viral replication and assembly[11].

## SEROTYPES AND PHYLOGENETICS OF HRVS

Serotypes are defined as groups within a single species of microorganisms that share distinctive surface structures. The four capsid proteins of HRVs provide the virion an icosahedral structure, with a canyon in VP1 of attachment to cell surface receptors. More than 90% of known HRV serotypes are classified as major group, utilizing the cell surface receptor intercellular adhesion molecule 1 (ICAM1), while the minor group HRVs attach cells *via* the low-density lipoprotein receptor (LDLR). Some of the major-group HRVs can use heparan sulphate as an additional receptor for cell attachment and entrance[16-18]. More than 100 serotypes of HRVs were discovered and the

diversities of serotypes of HRVs make the specific vaccine against the virus infection very difficult to create.

Phylogenetics is the study of the evolutionary relatedness among organisms. Molecular phylogenetics applies sequence data to infer these relationships. Based on sequence, phylogenetic sequence HRVs are classified into three species, HRV-A, HRV-B and HRV-C. HRV-A (containing 77 serotypes) and HRV-B (containing 30 serotypes) species can be cultured in normal cells culture[19]. HRV-C strains do not grow in standard cell culture although the genomic organization of HRV-C strains is similar to that of HRV-A and HRV-B. At least 50 different types of HRV-C have been identified [20,21]. In 2011, HRV-C was found to grow in sinus mucosal tissue, and the species used a distinct cell attachment mechanism[22]. It was then identified that HRV-C entrance of cells by cadherin related family member 3 (CDHR3) receptor[23].

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## RECEPTORS FOR HRVS

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### ICAM1

ICAM1 is a cell surface ligand for the lymphocyte function antigen 1 adhesion receptor [24,25]. It was cloned and sequenced in 1988[26]. ICAM1 is a 90 kD inducible surface glycoprotein. It promotes adhesion in immunological and inflammatory reactions. In 1989, ICAM1 was then found as a receptor for HRVs major group entrance to the cell by using ICAM1 monoclonal antibody blocking the cytopathic effect in HeLa cells[27]. It binds to integrins of CD11a/CD18, or CD11b/CD18 and it is a prominent molecule in leukocyte trafficking, immunological synapse formation, and cellular immune responses[28]. ICAM1 is expressed on essentially all leukocyte subsets, epithelial cells, endothelial cells, fibroblasts, platelets and others[29]. For most cell types under non-inflammatory conditions, ICAM1 expression is constitutively low, it is detectable only on endothelial cells[30,31]. On the condition of stimulations of IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$  and other cytokines, ICAM1 can increase expression in a cytokine- and cell-specific manner [28,32]. Soluble ICAM1 can be detectable in the plasma and it increases in patients with various inflammatory conditions. HRVs upregulate membrane-bound ICAM1 expression *via* a NF $\kappa$ B-dependent mechanism[33] and downregulate the release of soluble ICAM1[34]. ICAM1 upregulation was also founded *in vivo* on nasal epithelial cells in an experimental HRV39 infection of healthy volunteers[35].

### LDLR

LDLR family members were identified as the receptors for minor group rhinoviruses, that consists of only 12 known HRV-A types. The members are evolutionarily ancient proteins that are expressed on the surface of many cell types[36]. The LDLR family includes at least three members that can bind and internalize HRV as the LDLR, the LDLR related protein and the very low density lipoprotein receptor. Receptors in this family are recognized by the presence of several structural modules and overall similar domain arrangements. The structural characters include ligand-binding repeats, epidermal growth factor precursor repeats, a single transmembrane domain,  $\beta$ -propeller modules and a relatively short cytoplasmic tail[37]. LDLR uptakes its natural ligand, cholesterol-carrying lipoprotein particles by endocytosis, and their release upon delivery to the low pH milieu of the endosome[38]. The cytoplasmic tail of the LDLR family members contains specific motifs that can interact with a number of cytoplasmic adaptor and scaffold proteins to mediate signal transduction[37].

### CDHR3

CDHR3 is a member of cadherin superfamily of transmembrane glycoproteins. The biological function remains unclear. Other members of this family such as desmosomal cadherins and classical cadherins are responsible for communications between identical cells through calcium-dependent interactions. Protocadherins are involved in neuronal plasticity and tissue development[39]. Cadherins are the major components of adherens junctions and desmosomes and also have other functions including signalling and mechanical transduction[40].

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## OTHER RECEPTORS

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Some major-group HRVs also use heparan sulphate as an additional receptor[11]. Airway epithelial cells infected by HRV can detect and respond to the virus *via* toll-

like receptors (TLRs) to activate signalling pathways and generate pro-inflammatory cytokines and type I interferons[41]. The HRV6 capsid was found to be recognized *via* TLR2. With HRV6 ssRNA internalization, the virus genome is recognized by endosomally located TLR7 and TLR8[42].

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## HRV INFECTION AND RESPIRATORY DISEASES

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HRVs not only are highly associated with asthma, COPD and cystic fibrosis, the viruses also have been found to cause upper respiratory infection including common cold, acute otitis media and rhinosinusitis. They can be responsible for lower respiratory infection including cough, bronchiolitis, community-acquired pneumonia. Based on antigenic cross-reactivity in serum neutralization tests, clinical isolates of HRV-A and HRV-B identified by 1987[43] were classified into 100 serotypes. More recently isolated A and B types were assigned solely on sequence identity criteria[44], HRV-A and HRV-C isolates are more virulent in infants, and are more likely to cause exacerbations of childhood asthma compared to HRV-B[45,46]. HRVs cause respiratory illness throughout the world and throughout the year. Longitudinal studies of the epidemiology and clinical features reported a peak incidence of HRV infection in the early fall and a smaller peak in the spring[47]. HRVs are the most common cause of respiratory viral illness during the spring, summer, and fall months. Infections with influenza virus and RSV predominate in the winter[11]. Not like other respiratory viruses, such as influenza virus and respiratory syncytial virus that cause cytopathology of the upper respiratory tract; for HRV infection, the epithelial cell lining and borders remained structurally intact although the cells were sloughed[48]. However, HRVs can still cause damage of epithelial cell barrier function[49], which can facilitate the transmigration of bacteria and exposing basolateral epithelial cell receptors such as TLRs[50]. Direct infection of the lower airway or the stimulation of inflammatory, immunological, or neurogenic mechanisms are the mechanisms of low airway dysfunction or diseases. Impaired innate and acquired immune responses for Th1 responses were found in asthma patients[51,52]. Epidermal growth factor (EGF) promotes viral replication by suppressing antiviral related immune mediators and has prominent role of EGF in the immune response to HRVs[53]. There are currently no approved antiviral therapies for HRVs, and treatments majorly are supportive.

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## *ORMDL3* AND HRV INFECTION

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After the association of the polymorphism of *ORMDL3* and asthma has been established[2,54], the subsequent research found it was linked to the frequency of rhinoviral wheezing illness and then subsequent development of childhood asthma [6]. Inhalation allergen could induce a significant increase in levels of expression of *ORMDL3* in airway epithelium and in macrophages in an allergen-induced mouse model[55]. The research on the roles of *ORMDL3* in HRV infection just begun and most results were from mouse models and cellular models. In a transgenic mice that express increased levels of human *ORMDL3* showed that *ORMDL3* contributes to antiviral defence to HRV infection through pathways that may include interferons (IFN $\alpha$ , IFN $\beta$ , IFN $\lambda$ ), OAS, and RNase L[56]. In a human epithelial cell model, *ORMDL3* was found to be required in supporting HRV replication *via* SPT inhibition [57]. Human *ORMDL3* is a trans-membrane protein anchoring in the endoplasmic reticulum (ER). The ER is the site responsible for protein folding, storage of calcium and synthesis of lipids. ER stress can reduce the capacity for protein folding and thereby regulate cellular responses to inflammation. *ORMDL3* facilitates the unfolded protein response to cellular stress by influencing ER calcium ATPase and ER-mediated Ca<sup>2+</sup> flux[58]. It interacts with the serine SPT enzyme complex in sphingolipid synthesis especially for ceramide and sphingosine-1-phosphate (S1P) levels[59]. *ORMDL3* could work in multiple pathways in regulating HRV infection[60].

## THE POTENTIAL REGULATING MECHANISMS OF *ORMDL3* FOR HRV INFECTION

### **Regulating ICAM1 expression levels**

To explore the roles of *ORMDL3* in epithelial cells, our lab established *ORMDL3* knockdown and *ORMDL3* over-expression immortalised epithelial cell lines and human primary bronchial epithelial cells. Knockdown of *ORMDL3* led to a steroid-independent reduction of both IL8 and IL6 release and reduced ER stress after stimulation of IL1 $\beta$ . Global gene expression analysis revealed that knockdown of *ORMDL3* resulted in the reduction of expression of genes regulating host-pathogen interactions, stress responses and ubiquitination. Metabolomic analyses showed that knockdown led to changes in levels of metabolites integral to glycolysis. Additionally, knockdown increased concentrations of the immune mediators such as ceramides. The multiple effects of *ORMDL3* in cellular inflammation are consistent with its substantial genetic influence on childhood asthma. Of particular interest is that *ORMDL3* knockdown strongly reduced expression of the HRV receptor ICAM1 during the inflammatory response[61]. In an eosinophil *ORMDL3* knockdown experiment, a significant reduction in adhesion of *ORMDL3*-siRNA-treated eosinophils to ICAM1 was noted compared to control-siRNA-treated cell, and *ORMDL3* regulates eosinophil trafficking, recruitment[62]. The results indicate *ORMDL3* can regulate ICAM1 expression level, then influence HRV infection in human epithelial cells and immune cells.

### **Regulating ER stress**

*ORMDL3* is a protein anchored on the ER of the cell. The ER in eukaryotes is the site of protein folding as well as the site for synthesis of lipids and sterols and the storage of free calcium. Stresses on ER can therefore lead to an imbalance between the capacity for protein folding and the demand. It is linked to cellular responses to inflammation. ER stress happens when the capacity of the ER to fold proteins becomes saturated. ER stress induces the evolutionarily conserved signalling pathways, defined as the unfolded protein response, which compromises the stimulus and then determines whether the cell die or survives. It may be caused by factors that impair protein glycosylation, disulphide bond formation, mutations or overexpression. We previously experiments showed *ORMDL3* was a regulator of ER stress in mouse and in cellular models[61,63]. There are three signal transduction pathways for ER stress, including protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1)[64]. Both non-structural protein 2B and HRV16 can induce an ER stress response through the PERK and ATF6 pathways[65]. Different viruses can modulate these mechanisms to escape the host immune response to their advantages[66].

### **Regulating sphingolipids metabolism**

*ORMDL3* was first identified as a regulator for *de novo* synthesis of sphingolipids in cells[59]. Sphingolipids are amphipathic molecules derived from sphingosine. Ceramides are the central molecules of sphingolipids metabolism. Sphingosine phosphorylation leads to S1P. S1P and ceramides mediate cell proliferation, survival, apoptosis, differentiation and cell-cycle arrest[67,68]. Ceramide-rich platforms affect signalling cascades in immune cells, including activation of B cells, bacterial pathogen infection. S1P drives the differentiation of immune cells, inducing changes in their phenotypes and regulating production of eicosanoids and inflammatory cytokines [69]. Clinical studies showed that sphingosines and ceramide were increased in asthmatic airways[70]. Sphingolipid pathways offer many opportunities for pharmacologic intervention and investigations of anti-inflammatory effects have been centred on S1P[69]. Importantly, modulating sphingolipids is known to affect ICAM1 expression in epithelial cells (keratinocytes)[71] so that the ICAM1/sphingolipid axis may provide novel prevention strategies for viral-induced childhood asthma. Ceramide levels were greatly affected by the expression of *ORMDL3* in mouse model [72,73] and in airway epithelial cells[61]. Decreased sphingolipid synthesis was found in children with 17q21 asthma-risk genotype[74]. Ceramides activate protein phosphatase 2 to cause endothelial dysfunction[75]. Ceramides suppress the electron transport chain to induce production of reactive oxygen species in mitochondria[76]. Imbalance of ceramides and impaired TLR4-mediated autophagy were reported in an *ORMDL3*-overexpressing mouse model[77]. S1P receptors inhibition was found to be critical for immunomodulation. S1P can directly suppress TLR mediated immune response from T cells. S1P extracellular actions are mediated by its interaction with a

family of five specific G-protein-coupled receptors, S1P<sub>1</sub>-S1P<sub>5</sub>[78]. Ceramide kinase and sphingosine kinases control many aspects of cell physiology, including inflammatory response and cell survival[79]. S1P was found to be important in immunoglobulin E-mediated mast cell migration and degranulation[80], allergic asthma, and secretion of inflammatory cytokines[81]. In allergic models of asthma, S1P and ceramide are important signalling molecules for airway hyperreactivity, mast cell activation, and inflammation[82].

### **Regulating ER-Golgi interface**

Golgi apparatus is a cell organelle that facilitates process and package proteins and lipid molecules to be exported from the cell. Infection of human epithelial cells with several rhinovirus strains triggers a rapid activation of the acid sphingomyelinase. The activity of the acid sphingomyelinase results in the formation of ceramide in the cell membrane. Acid sphingomyelinase is also a key molecule for the infection of human cells with rhinoviruses[83,84]. The ability of replicating picornaviruses to influence the function of the secretory pathway has important implications for host defence. Individual non-structural protein B2 and HRV16 can both fragment the Golgi apparatus and block secretion, whereas viral infection fragments the Golgi apparatus without blocking secretion[84]. HRV uses a phosphatidylinositol 4-phosphate/cholesterol counter-current for the formation of replication compartments at the ER-Golgi interface[85]. *ORMDL3* regulates ER stress and lipid membrane synthesis and that could directly influence ER-Golgi interface to response HRV infection.

### **Regulating glycolysis**

Glycolysis is a cytoplasmic pathway that breaks down glucose into two three-carbon compounds and generates energy. Glucose is trapped by phosphorylation, with the assistance of the enzyme hexokinase. Glycolysis is one of major energy-yielding pathways that glucose is converted into pyruvate in the glycolytic process[86]. Recent research showed that IL-1 $\beta$ /inhibitory  $\kappa$ B kinase  $\epsilon$  signalling plays an important role in house dust mite-induced glycolysis[87]. Aerobic glycolysis is increased in asthma, which promotes T cell activation. Inhibition of aerobic glycolysis blocks T cell activation in asthma[88]. Lactic acid (LA), pyruvic acid (PA) and LA/PA are increased in the process. Increased glycolysis and anaerobic respiratory muscle glycolysis during airways obstruction may be important in these changes[89]. The early asthmatic response has been found to be associated with calcium binding, glycolysis and mitochondria activity in rats[90]. Glycolysis of target cells was found as an intrinsic host factor that determines the extent of norovirus replication[91]. *ORMDL3* deficient epithelial cells showed abnormality of glycolysis[61] and that can regulate HRV replication in cytoplasm.

The possible regulating mechanisms of *ORMDL3* for HRV infection were listed in the Table 1.

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## **THE POTENTIAL THERAPEUTIC TARGETS FOR HRV INFECTION**

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### **Targeting *ORMDL3/ICAM1* and sphingolipid pathways**

Many compounds work in the *ORMDL3/ICAM1* and sphingolipid pathways. Myriocin is the potent inhibitor of SPT, the rate-limiting enzyme of first step in sphingosine biosynthesis. Recent research showed that SPT activity was increased by house dust mite exposure and that *de novo* sphingolipids synthesis can be effectively inhibited by myriocin both *in vitro* and *in vivo*[92]. Fumonisin B1 has a structural similarity to the cellular sphingolipids, and this similarity can disturb the metabolism of sphingolipids by inhibiting the enzyme ceramide synthase[93]. Fumonisin B1 can attenuate nitrotyrosine formation and oxidative/nitrosative stress, epithelial cell apoptosis, and airway inflammation to improve histopathological abnormalities[94]. Tamoxifen inhibits ceramide glycosylation[95]. Tamoxifen treatment in horses with induced acute pulmonary inflammation promoted early apoptosis of blood and BALF neutrophils, reduction in BALF neutrophils[96]. Fingolimod is an FDA approved immunomodulatory drug for treating multiple sclerosis by down regulating S1P receptor[97]. FTY72 acts as a high-affinity agonist at the G protein-coupled sphingosine 1-phosphate receptor-1 (S1P1) on thymocytes and lymphocytes to induce aberrant internalization of the receptor[98]. There are numerous inhibitors in sphingolipid and ceramide synthesis pathways[99,100], investigating these inhibitors provide the potential therapeutic tools to influence HRV infection. HRV-induced inflammatory responses are inhibited by phosphatidylserine containing liposomes[41].

**Table 1 Orosomucoid-like protein 3 roles in regulating human rhinovirus infection**

Regulating molecules and processes	The roles in human rhinovirus infection	Ref.
ICAM1	<i>ORMDL3</i> regulates ICAM1 expression for influencing HRV adhesion and entrance and viral load	[56,61,62]
ER stress	<i>ORMDL3</i> regulates ER stress and the ER stress can induce PERK and IRE1 pathways that affect HRV infection	[61,63,65]
Ceramide and S1P	<i>ORMDL3</i> regulates ceramide and S1P levels. S1P and ceramide are responsible for cell survival, proliferation, apoptosis, differentiation and cell-cycle arrest; they also affect ICAM1 expression	[55,61,71,72,77]
ER-Golgi interface	HRV can both fragment the Golgi apparatus and block secretion. <i>ORMDL3</i> regulates ER-Golgi interface through ER stress and sphingolipid metabolism	[61,84,85]
Glycolysis	<i>ORMDL3</i> regulates glycolysis. Glycolysis can determine the extent of replication of HRVs in cells	[61,91]

ICAM1: Intercellular adhesion molecule 1; *ORMDL3*: Orosomucoid-like protein 3; HRV: Human rhinovirus; ER: Endoplasmic reticulum; S1P: Sphingosine-1-phosphate.

### Research models of epithelial cells and finding new targets for HRV infection

Research models to investigate interactions between human host (genetic) and environmental factors are underdeveloped. These interactions are very important for chronic respiratory diseases such as asthma. We now know that airway microorganisms play important roles in health and in chronic respiratory diseases, but how the host and microorganisms function remain unclear. The airway epithelium has previously been investigated with monolayer models, where undifferentiated epithelial cells are grown underneath culture media. Cells that are grown at an air liquid interface (ALI) can be fully differentiated. ALI becomes a realistic and efficient tool to study cell-cell interaction studies following exposure to aerosolized or gaseous form of air pollutants[101], bacteria[102] and virus[103]. Primary bronchial epithelial cells cultured at ALI leads to differentiate into respiratory epithelium consisting of goblet cells, ciliated cells, basal cells and club cells. ALI culture system is also considered as a feasible approach to implement the "3R principle"-replacement, reduction, Recently epithelial ALI culture was successfully applied with HRV infection [104]. ALI cultures contain more epithelial components and are closer to normal human airways. In a further development, three-dimensional (3D) cultured lung tissues known as spheroids[105] other cell types such as fibroblasts are included. 3D culture with epithelial cells could help to provide highly predictive drug tests for patient-specific conditions in the near future[106]. The advantages of the ALI and 3D human lung spheroid models for interaction study are listed in Table 2. Importantly, ALI and 3D human lung spheroid models can be co-cultured with microorganisms relevant to asthma. These models provide an alternative of animal research and will reduce the use of animals in experiments as animal model for genetic modify are complicated procedures and time-consuming. Genetic animal model usually takes many generations of breeding and screening. For example, we identified *DPP10* as a novel gene underlies asthma in 2003[107], we created a *Dpp10* mutagenesis mouse tool and finally finished functional studies in 2018[108]. The use of genetic modified epithelial cells such as specific gene knockout cells not only provides a powerful platform to study the interaction between gene and environment but also to identify the novel therapeutic targets such as for HRV infection.

## CONCLUSION

*ORMDL3* emerged as a key molecule to regulate HRV infection in human respiratory epithelial cells. It influences the expression of HRV receptor ICAM1, the ER stress pathway, ceramide and S1P metabolism, ER-Golgi interface and glycolysis process. *ORMDL3*/ICAM1 and sphingolipid metabolism provide novel therapeutic targets for HRV infection. Epithelial models with ALI and other 3D cultures will have prominent roles to identify the druggable molecules for clinical treatment of asthma, COPD, cystic fibrosis and other respiratory conditions induced by HRVs.

Table 2 The models for studying interaction of host and environmental factors

The available models	Advantages	Disadvantages
Monolayer cell models	Simplistic model; Easy to culture within short times	Cells underneath the medium, no connection to other types of cells and no tight junctions; Non-optimal physiologic response; The growth kinetics of bacteria, fungal or virus on monolayer are known to be different from human body
Air liquid interface model	Polarized differentiated airway epithelium containing ciliated epithelial cells, basal cells and mucus producing cells, mimicking human epithelium; It can be co-cultured with pathogens; Respiratory virus is known to show similar replication kinetics as in human body	
3D human lung spheroid model	3D multicellular spheroids are small, tightly bound cellular aggregates that tend to form when cells are maintained under non-adherent conditions; Other cell types such as fibroblasts can be incorporated and can be co-cultured with pathogens	
Animal models	<i>In vivo</i>	Have ethical issues and many results cannot be replicated in human studies; High cost; Time consuming, not applicable to high-throughput studies

3D: Three-dimensional.

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